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EXAMINER	
BALLS, ROBERT J	

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BEFORE THE BOARD OF PATENT APPEALS

AND INTERFERENCES

Application Number: 10/663,533
Filing Date: September 16, 2003
Appellant(s): GILBERT ET AL.

Wendy Choi

For Appellant

REVISED EXAMINER'S ANSWER

This Revised Examiner's Answer is in response to Applicant's appeal brief filed on April 11, 2005 and replaces the Examiner's Answer filed on July 11, 2005, which is vacated in accordance with The Board of Patent Appeals and Interferences' Order Returning Undocketed Appeal to Examiner.

Table of Contents

(1) REAL PARTY IN INTEREST

Appellants' brief identifies Wyeth as the real party in interest.

(2) RELATED APPEALS AND INTERFERENCES

Appellants' brief states there are no related appeals or interferences pending. The Board, however, may in its discretion require an explicit statement as to the existence of any related appeals and interferences.

(3) STATUS OF CLAIMS

Claims 1 – 25 and 27 – 32 are cancelled. Claims 26 and 33 – 52 are rejected. There are no claims allowed, withdrawn, or presently under objection. The rejection of claims 26, 33 – 52 stand or fall together. Appellants' brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. 37 CFR 1.192(c)(7).

(4) STATUS OF AMENDMENTS

The December 20, 2004 Amendment After Final Rejection has been entered.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Claims 26 and 33 – 52 are directed to a method of treating a subject suffering from a condition selected from Alzheimer's disease, appetite control, disorders of thermoregulation, and sleep dysfunction, comprising the step of providing to said

subject an effective amount of a compound of formula I, wherein formula I is described in the specification on page 1, line 26 to page 3, line 10.

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 26, 33-52 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

The Board or Patent Appeals and Interferences must determine whether claims are properly rejected for failing to meet the requirements of 35 U.S.C. §112 when the claims encompass a broad genus of chemical compounds directed toward treating a multitude of unrelated diseases by contradicting physiological processes absent any evidence demonstrating such compound exists.

(7) ARGUMENT

A. Grounds of Rejection

Claims 26, 33-52 contain subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). Courts rely on the following factors set out in *In re Wands* to determine whether undue experimentation is required to practice a claimed invention, i.e. whether the claimed invention is enabled: (a) The breadth of the claims; (b) The nature of the invention and predictability in the art; (c) The state of the prior art; (d) The level of one of ordinary skill; (e) The amount of direction provided by the inventor; (f) The existence of working examples; and (g) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *Id.* The analysis must include consideration of all factors. It is improper to rely on only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407.

(a) The Breadth of the Claims

The claims are broad due to the high number of compounds and diseases they embody. Formula I encompasses many different compounds due to the breadth of its variables (i.e. R^1 and R^2). Applicants assert that these numerous compounds are effective in treating a variety of unrelated diseases: Alzheimer's disease, appetite control (including the conflicting hyperphagia and hypophagia), any disorder of thermoregulation (including the opposing hypothermia and hyperthermia), and any sleep dysfunction (including the conflicting insomnia and narcolepsy).

(b) The Nature of the Invention and Predictability in the Art

The invention is physiological in nature as it is directed toward pharmaceuticals and treating diseases with those pharmaceuticals, an art which is highly unpredictable. "[T]he scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). In the highly unpredictable pharmaceutical art, the required disclosure is greater than for the disclosure of an invention involving predictable factors such as mechanical or electrical elements. *In re Vaeck*, 20 USPQ 2d 1438 (CAFC 1991). The high degree of unpredictability is well recognized in the $5HT_{1A}$ receptor ligand art. For example, a slight change in the structure of a compound can drastically alter its affinity and selectivity. Wijngaarden, *Recl. Trav. Chim. Pays-Bas*. 112:126-130 (1993), pages 129-130, Fig. 6, Fig. 7, Fig. 8. *In vitro* binding data do not necessarily reflect the *in vivo* activity under the much more complex physiological conditions. *Id.* Since the above studies (and the studies described Lanfumey et al., *Curr. Drug Targets–CNS & Neurological Dis.* 3:1-10 (2004) and Kwon et al., *Neurodegenerative Dis.* 1:113-52 (2004)) are based on $5HT_{1A}$ antagonists that are structurally different from the instant compounds, one of ordinary skill in the art has little basis to extend the data in these references to the instant. These studies demonstrate the complex nature of the $5HT_{1A}$ art and the high degree of unpredictability it entails.

(c) The State of the Prior Art

The prior art fails to show a relationship between $5HT_{1A}$ agonists and all of the claimed diseases. Although some $5HT_{1A}$ agonists have anxiological and antidepressant activity, the nexus between Alzheimer's disease, appetite control, disorders of thermoregulation, sleep dysfunction, and $5HT_{1A}$ receptor antagonism is not established. For example, while $5HT_{1A}$ receptor agonist evokes hypothermia, inhibition of $5HT_{1A}$ synthesis and $5HT_{1A}$ lesions do not prevent hypothermia in rats (Barnes et al. *Neuropharmacology*, 38:1083-1092 (1999), page 1092). Some of the responses elicited by the $5HT_{1A}$ receptor agonist 8-OH-PAT, such as hyperphagia (Fletcher et al., *Psychopharmacology*, 100(2):188-94 (1990), abstract), and altered sexual behavior (Matuszewich et al., *Brain Research*, 820(1-2):55-62 (1999), abstract), are not reversed by a $5HT_{1A}$ receptor antagonists, thereby suggesting that these effects are not mediated by the $5HT_{1A}$ receptor and that the agonism/antagonism relationship is not straight-forward and predictable. The prior art shows that there is no umbrella drug known to be effective in treating all the diseases/conditions claimed and demonstrates a lack of relationship between the claimed compounds and the diseases for which they are intended to treat.

(d) The Level of One of Ordinary Skill

The art requires a high level of skill to perform. $5HT_{1A}$ receptors have subclasses differing in their structures, regional distribution, pharmacology, modes of actions, and functions (Wijngaarden et al.; Barnes et al., pages 1085-6).

(e) The Amount of Direction Provided by the Inventor

The evidence fails to show that the claimed compounds are capable of treating the claimed diseases. The specification merely discloses how to synthesize the claimed chemical compounds and provides $5HT_{1A}$ transporter binding assays, $5HT_{1A}$ receptor binding assays, and assays for the assessment of antagonist activity (see specification pages 9-10). Results are shown for Examples 1-11 on page 11 of the specification.

(f) The Existence of Working Examples

No working example exists showing that a claimed compound is effective at treating all the claimed diseases.

(g) The Quantity of Experimentation Needed to Make or Use the Invention Based on the Content of the Disclosure

The quantity of experimentation necessary to make or use the disclosed invention is high based on the breadth of the claims, the unpredictability of the art, the limited guidance in the specification, and the high skill required to practice the claimed invention. A person of ordinary skill in the art would be subjected to undue experimentation in order to make and use the invention, and therefore, the invention is not enabled.

B. Response to Applicants' Arguments

a. The Nexus Between $5HT_{1A}$ Receptor Antagonists and the Treatment of Alzheimer's Disease, Appetite Control, Disorders of Thermoregulation and Sleep Dysfunction

The nexus between the treatment of the claimed diseases and the antagonism of $5HT_{1A}$ receptor has not been predictably established, especially in view of the findings of Barnes et al. Barnes et al. shows that $5HT_{1A}$ receptor agonists may evoke hypothermia but conversely, $5HT_{1A}$ agonists do not prevent hypothermia in rats (Barnes et al., page 1092). Some of the responses elicited by the $5HT_{1A}$ receptor agonist 8-OH-PAT such as hyperphagia (Fletcher et al., abstract) and altered sexual behavior (Matuszewich et al., abstract) are not reversed by a $5HT_{1A}$ receptor antagonists, thereby suggesting that these effects are not mediated by the $5HT_{1A}$ receptor and simple agonism/antagonism at the $5HT_{1A}$ receptor is not predictive of disease outcome *in vivo*.

Appellants have not addressed the above reference. Instead, they cite the following references: (1) Lanfumey et al. and Kwon et al. to support a claim for Alzheimer's disease (published in 2004, which is after the instant effective filing date); (2) Moreau et al., *Brain Res. Bull.* 26(6):901-4 (1992) to support a claim directed to appetite control; (3) Ootsuka et al., J. Physiol. 552(1):303-14 (2003) to support a claim directed toward disorders of thermoregulation; and (4) Sorensen et al., *Behav. Brain Res.* 121(1-2):181-7 (2001) to support a claim directed toward sleep dysfunction. These references do not teach how the $5HT_{1A}$ receptor is involved in these diseases and fails to show that antagonism of $5HT_{1A}$ would have a predictable, therapeutic outcome on the diseases and symptoms encompassed by the claims.

(1) Lanfumey et al. and Kwon et al. were published after the effective filing date and are not considered.

(2) Moreau et al. teach that $5HT_{1A}$ activation may decrease palatable food consumption in rats. Although the reference may support a claim drawn to decreasing palatable food intake, it does not support the present claims drawn to all types of 'appetite control' including both hyperphagia (abnormally increased appetite for and consumption of food) and hypophagia (abnormally decreased appetite for and consumption of food).

(3) Ootsuka et al. teach that $5HT_{1A}$ activation may abolish body temperature decrease. Although this reference may support a claim drawn to hypothermia, it does not support the present claims drawn to any 'disorders of thermoregulation,' which includes the opposing hypothermia and hyperthermia.

(4) Sorensen et al. teach that $5HT_{1A}$ activation may induce a decrease in REM sleep. Although this reference may support a claim drawn to narcolepsy, it does not support the present claims drawn to all types of 'sleep dysfunction,' which covers both insomnia and narcolepsy.

Since the claims recite broad general classes of diseases embracing opposing and conflicting conditions arising from diverse origins, one of ordinary skill in the art would not reasonably expect to use a single $5HT_{1A}$ receptor antagonist compound to treat all the contradictory disorders encompassed by the instant claims.

With the filing of this Brief, Appellants have submitted ***seven new references***, which should have been submitted in the earlier stages of the prosecution. Nonetheless, these references fail to provide the required support for the following reasons.

Reference 1: Applicants site Schechter et al., *Curr. Pharm. Design*, 8:139-145 (2002) to support claims directed toward Alzheimer's Disease. However, this reference was published after the effective filing date and is therefore not reflective of the state of the art. Further, Schechter et al. only describes the ***potential*** use of $5HT_{1A}$ receptor antagonists to treat cognitive dysfunction associated with Alzeheimer's disease.

References 2 & 3: Applicants site Ebenezer et al., *Physil. Behav.* 67(2):213-7 (1999) to support claims directed toward appetite control. Ebenezer et al. teaches that the $5HT_{1A}$ agonist 8-OH-DPAT causes a hyperphagic effect on satiated pigs and a hypophagic effect on fasted pigs. Furthermore, $5HT_{1A}$ antagonist WAY 100635 reverses the effects. WAY 100635 by itself, however, has no significant effects on feeding, which is different from the findings of Moreau et al., who show that the $5HT_{1A}$ antagonist (S)-UH-301 decreases palatable food consumption. These references highlight the unpredictability of the art and caution the extrapolation of results from one antagonist to another.

References 4 & 5: . Applicants site Brubacher et al., *Vet. Hum Toxicol.* 38(5):358-61 (1996) to support claims directed to disorders of thermoregulation. Brubacher et al. teach that excessive stimulation of $5HT_{1A}$ leads to the excess serotonin associated with hyperthermia Applicants have not shown that $5HT_{1A}$ antagonists would abolish this effect. Brubacher et al.'s disclosure contradicts Oerther et al., *Neuroreport.*,

11(18):3949-51 (2000), who teach that hypothermia is caused by the $5HT_{1A}$ agonist 8-OH-DPAT.

References 6 & 7: Applicants site Bjorvatn et al., *Rev. Neurosci.* 9(4):265-73 (1998) and Gillin et al., *Psychopharmacology* (Berl.) 116(4):433-6 (1994) to support claims directed to sleep dysfunction. While Bjorvatn et al. demonstrates that systemic administration of $5HT_{1A}$ agonist increases wakefulness and reduces slow wave sleep and REM sleep, and Gillin et al. show that a relatively selective $5HT_{1A}$ agonist, ipsapiraone, inhibits REM sleep, the references do not show the opposite effect, i.e. that these compounds are capable of inducing sleep. In view of these references, one of ordinary skill in the art would not use a $5HT_{1A}$ antagonist to both increase and decrease sleep. Bjorvatn et al. even states that although $5HT_{1A}$ has been implicated in the regulation of vigilance, whether $5HT_{1A}$ is important for sleep or waking processes remains controversial (Bjorvatn et al., abstract, first sentence).

Since the claims recite broad general classes of diseases embracing opposing and conflicting conditions arising from diverse origins, one of ordinary skill in the art would not reasonably expect to use a single $5HT_{1A}$ receptor antagonist compound to treat all the contradictory disorders encompassed by the instant claims.

b. Treating Conditions that Encompass Seemingly Opposite Characteristics With the Same Compound

Appellants submit that it is not illogical to treat opposing conditions with the same compound and that it is widely recognized that a compound may serve to restore or ensure homeostasis with respect to a given physiological system. Undoubtedly, negative feedback is an important part of homeostasis. In some cases, a single

compound can act as both an agonist and an antagonist and is useful in treating conflicting conditions. In the instant case, however, there is no evidence showing that the claimed compounds are capable of treating opposing diseases. Conversely, the prior art demonstrates the opposite is true; that these compounds generally do not evoke opposing results. Furthermore, the specification fails to disclose any guidance or direction demonstrating how to use the claimed compounds to treat opposing diseases. Those of ordinary skill in the art recognize that single compounds capable of treating opposing symptoms are highly condition specific—a slight change in conditions can have dramatic effect on the body's physiological response to that compound. The different critical conditions required to achieve opposite responses have not been described in the specification nor disclosed in the prior art. Therefore, in the absence of more guidance setting forth the condition required to treat opposing symptoms, one of ordinary skill in the art would be subjected to undue experimentation in order to practice the invention as claimed.

c. The Sufficiency of Representative Examples Establishing Compounds of Formula I as $5HT_{1A}$ Receptor Antagonists

Appellants submit that the two disclosed assays (3H-paroxetine binding assay and [^{35}S]-GTPγS binding assay) show that the compounds of formula I are capable of treating all of the conflicting diseases encompassed by the claims. However, these assays merely demonstrate that compounds of formula I are involved in $5HT_{1A}$ binding, nothing more. As demonstrated previously, there is a high degree of unpredictability in the $5HT_{1A}$ receptor antagonist art and compounds of similar structure often exhibit very different biological activities. *In vitro* antagonism does not accurately predict *in vivo*

efficacy. Wijngaarden et al., pages 129-130, Fig. 6, Fig. 7, Fig. 8. One of ordinary skill in the art therefore would have little basis to extrapolate results from the tested compounds to other antagonist compounds of dissimilar structure.

The nexus between $5HT_{1A}$ receptor antagonists and treatment of Alzeheimer's disease, appetite control, disorders of thermoregulation and sleep dysfunction has not been predictably established. The breadth of the claims is not commensurate in scope with that of the objective enablement and the specification does not provide sufficient guidance and teaching to enable one of ordinary skill in the art to use the invention as claimed without undue experimentation.

For these reasons the rejections should be sustained.

(8) CLAIM APPENDIX

A copy of the appealed claims is attached hereto.

(9) EVIDENCE APPENDIX

Barnes et al. *Neuropharmacology*, 38:1083-1092 (1999).....7, 9

Brubacher et al., *Vet. Hum Toxicol.* 38(5):358-61 (1996).....11

Bjorvatn et al., *Rev. Neurosci.* 9(4):265-73 (1998)..... 12

Ebenezer et al., *Physil. Behav.* 67(2):213-7 (1999).....11

Fletcher et al., *Psychopharmacology*, 100(2):188-94 (1990).....7, 9

Gillin et al., *Psychopharmacology* (Berl.) 116(4):433-6 (1994)..... 12

Kwon et al., *Neurodegenerative Dis.* 1:113-52 (2004) 6, 9

Lanfumey et al., *Curr. Drug Targets–CNS & Neur. Dis.* 3:1-10 (2004).....6, 9, 10

Matuszewich et al., *Brain Research*, 820(1-2):55-62 (1999).....7, 9

Moreau et al., *Brain Res. Bull.* 26(6):901-4 (1992).....9, 10, 11

Oerther et al., *Neuroreport.*, 11(18):3949-51 (2000).....11

Ootsuka et al., J. Physiol. 552(1):303-14 (2003) 9, 10

Schechter et al., *Curr. Pharm. Design*, 8:139-145 (2002)..... 11

Sorensen et al., *Behav. Brain Res.* 121(1-2):181-7 (2001).....9, 10

Wijngaarden et al., *Recl. Trav. Chim. Pays-Bas.* 112:126-130 (1993).....6, 7, 14

(10) REATED PROCEEDINGS INDEX

There are no related proceedings.

Respectfully submitted,

Cecelia Tsang
Supervisory Patent Examiner
Art Unit 1625
February 23, 2006

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Commissioner for Patents

The appeal brief is not in accordance with 37 CFR §41.37(c)(1). Specifically, it does not include the headings, "Evidence Appendix" and "Related Proceedings Appendix." (See (9) and (10) below).

Appellants are hereby required to submit the missing "Evidence Appendix" and "Related Proceedings Appendix," as set forth in 37 CFR §41.37(c)(1)(ix) and 37 CFR §41.37(c)(1)(x).

To expedite prosecution, the examiner has considered the deficient appeal brief filed on April 11, 2005 and provided a Revised Examiner's Answer.

RJB

Notification of Non-Compliant Appeal Brief (37 CFR 41.37)	Application No. 10/663,533	Applicant(s) GILBERT ET AL.	
	Examiner James Balls	Art Unit 1625	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *11 April 2005* is defective for failure to comply with one or more provisions of 37 CFR 41.37.

To avoid dismissal of the appeal, applicant must file anamended brief or other appropriate correction (see MPEP 1205.03) within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☒ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, (e.g., rejected, allowed, withdrawn, objected to, canceled), or does not identify the appealed claims (37 CFR 41.37(c)(1)(iii)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 41.37(c)(1)(iv)).

4. ☐ (a) The brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters; and/or (b) the brief fails to: (1) identify, for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function under 35 U.S.C. 112, sixth paragraph, and/or (2) set forth the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification by page and line number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(v)).

5. ☐ The brief does not contain a concise statement of each ground of rejection presented for review (37 CFR 41.37(c)(1)(vi))

6. ☐ The brief does not present an argument under a separate heading for each ground of rejection on appeal (37 CFR 41.37(c)(1)(vii)).

7. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(viii)).

8. ☐ The brief does not contain copies of the evidence submitted under 37 CFR 1.130, 1.131, or 1.132 or of any other evidence entered by the examiner **and relied upon by appellant in the appeal**, along with a statement setting forth where in the record that evidence was entered by the examiner, as an appendix thereto (37 CFR 41.37(c)(1)(ix)).

9. ☐ The brief does not contain copies of the decisions rendered by a court or the Board in the proceeding identified in the Related Appeals and Interferences section of the brief as an appendix thereto (37 CFR 41.37(c)(1)(x)).

10. ☐ Other (including any explanation in support of the above items):

———.